

Stereocontrolled synthesis of thiohydantoin spironucleosides from sugar spiroacetals

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Dedicated to Professor J. Plumet on the occasion of his 60th birthday

Abstract—5-Epithiohydantocidin, *N*-alkyl and *N*-glycosylthiohydantoin spironucleosides are prepared from glycosylaminoesters and from furanoid and pyranoid methyl isothiocyanatoulosonates. The aminoesters and the isothiocyanates are obtained, in a stereocontrolled manner, from sugar spiroacetals through a high-yielding sequence involving ring opening with trimethyl azide, formation of an ester group, reduction of the azide, and, in the case of isothiocyanates, reaction with thiophosgene.

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1. Introduction

The chemistry of spironucleosides, a type of nucleoside in which the anomeric carbon belongs simultaneously to the sugar ring and to the nitrogenated heterocyclic moiety,¹ has received considerable development in the last decade. This interest is due to the isolation from culture broths of *Streptomyces hygroscopicus* of (+)-hydantocidin (**1**), the first natural spironucleoside.² The (+)-hydantocidin shows low toxicity for mammals and has herbicidal and plant growth-regulatory activities, which have been related to its inhibitory activity of adenylysuccinate synthase.³ Other spiro-anulated compounds⁴ also have biological interest due to their activity as inhibitors of glycogen phosphorylase and α -amylase.⁵ Syntheses of (+)-hydantocidin have been reported,⁶ and starting from 1993 many syntheses of hydantocidin analogues and related carbocyclic derivatives have been described.^{1b,7}

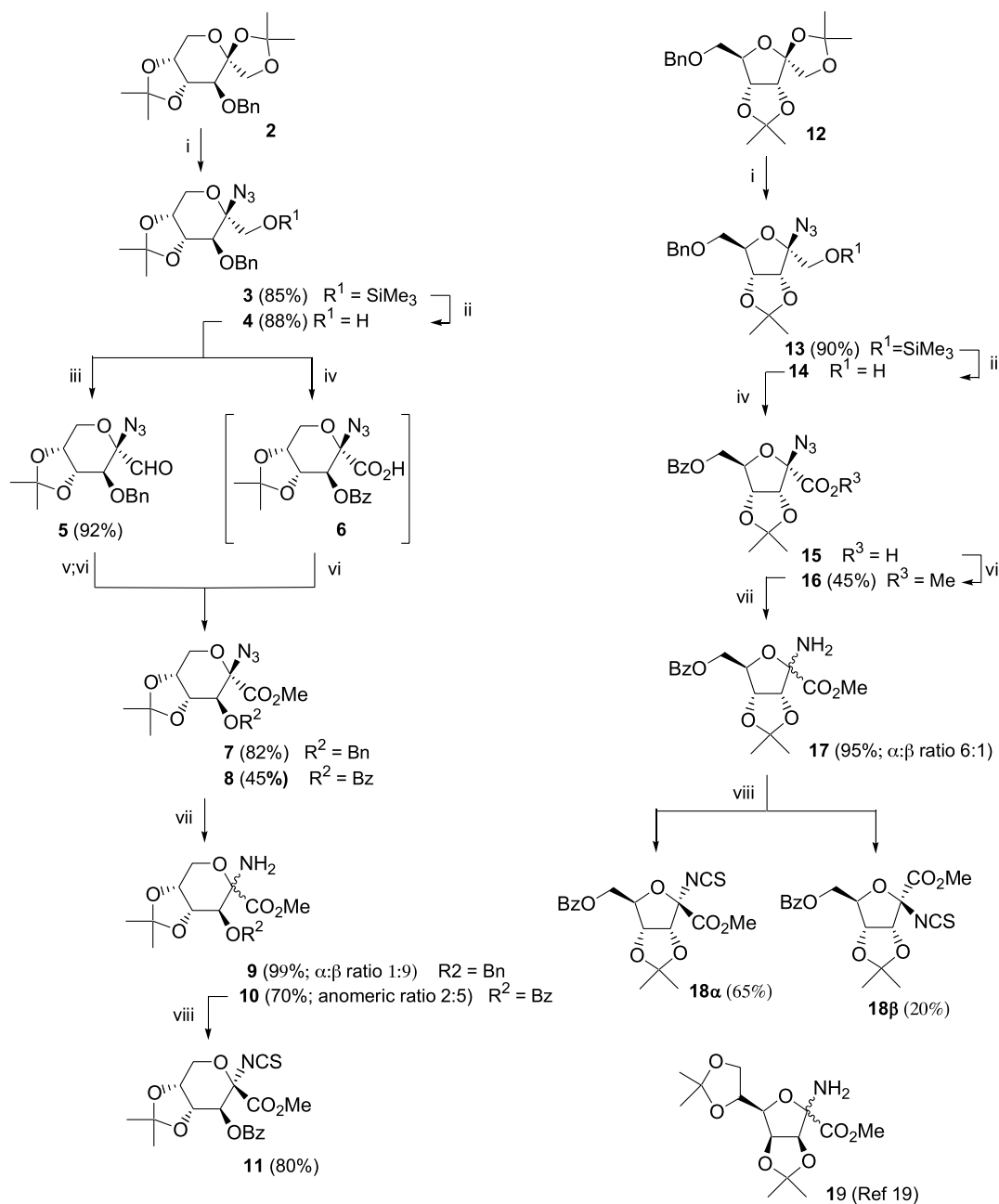
Recently, we reported our preliminary results on the preparation of pyranoid and furanoid isothiocyanatoulosonates, a new type of sugar isothiocyanate which is used for the stereocontrolled preparation of thiohydantoin spironucleosides.⁸ Some data on related ulosonitriles⁹ and furanoid ulosonoisothiocyanates¹⁰ have been reported later.

In this paper, we report the full data on a synthetic procedure to prepare furanoid and pyranoid spirothiohydantoin using methyl isothiocyanatoulosonates (**11**, **18**) and methyl aminoulosonates (**9**, **10**, and **17**) as key intermediates. We have previously shown^{7f} that ketofuranosyl isothiocyanates are transient intermediates in the preparation of spironucleosides of 1,3-*O,N* five member heterocycles.

2. Results and discussion

The starting materials to prepare the pyranoid and furanoid 2-isothiocyanatoulosonic esters **11** and **18** (Scheme 1) were the β -azido-1-trimethyl ethers **3** and **13**, respectively, which we have previously reported,^{7f} and were obtained by reaction of trimethylsilyl azide with the corresponding spiroacetal¹¹ **2** or **12** in freshly distilled acetonitrile, under stringently anhydrous conditions. Desilylation of **3** with a catalytic amount of TBAF (tetrabutyl ammonium fluoride). 3H₂O produced **4** in high yield. Swern¹² oxidation of **4** afforded the azido aldehyde **5**, whose NMR data showed the signals for **5** and additional signals corresponding to a hydrate as is described for related aldehydes.¹³ Further oxidation (NaClO₂) of **5** followed by treatment with diazomethane gave the 3-*O*-benzylazido ester **7**. Treatment of **4** with ruthenium chloride-sodium metaperiodate produced simultaneous oxidation of the formyl and benzyl groups with formation of the 3-*O*-benzoyl ulosonic acid derivative **6**, which was not isolated, and in situ converted (reaction with CH₂N₂) into the methyl 3-*O*-benzoyl azido

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Scheme 1. Preparation of new glycosyl aminoulosonates and glycosyl isothiocyanatoulosonates from sugar spiroacetals. Reagents and conditions: (i) TMSN₃, TMSOTf, CH₃CN, 0 °C; (ii) TBFA·3H₂O, THF, rt; (iii) DMSO, CH₂Cl₂, -70 °C; (iv) RuCl₃·H₂O, NaIO₄, CH₃CN, H₂O, CCl₄, rt; (v) NaClO₂, (CH₃)₂C=CH-CH₃, NaH₂PO₄·2H₂O, ^tBuOH, H₂O, 0 °C; (vi) CH₂N₂, Et₂O, MeOH, 0 °C; (vii) H₂/C-Pd, MeOH, rt; (viii) CSCL₂, CHCl₃, H₂O, CaCO₃, rt.

ester **8**. Catalytic hydrogenation of **7** and **8** gave the glycosylaminoester anomeric mixtures **9** and **10**, respectively, in good yields. The anomeric ratio for **9** was 1:9 (α : β , CDCl₃, rt, equilibrium), whereas in the case of **10** the ratio of the two anomers was 2:5 (same conditions), although the anomeric (C-2) configuration of each anomer for **10** was not determined. The anomeric mixture **9** was used only in route A (Scheme 2) for the synthesis of spirothiohydantoin. Compound **10** was also transformed, by reaction with thiophosgene in basic medium, into an anomeric mixture (α : β 16:1) of glycosyl isothiocyanates, from which only the α anomer **11** was isolated. This compound was used in route B of spirothiohydantoin (Scheme 2).

In a similar way, the reaction of **13** with TBAF·3H₂O gave the known^{6b} 1-*O*-unprotected furanosyl azide **14**, which by oxidation with ruthenium chloride–sodium metaperiodate (\rightarrow **15**), followed by esterification with CH₂N₂, produced the methyl ulosonate **16**. Catalytic hydrogenation of **16** yielded the anomeric mixture (α : β ratio 6:1) of aminoesters **17** in virtually quantitative yield. Reaction of **17** with thiophosgene in the presence of CaCO₃ gave, after column chromatography, the α (65%) and β (20%) isothiocyanato ulosonates **18 α** and **18 β** as isolated products.

Table 1 shows selected spectroscopic data for the structural assignments of compounds **4–5**, **7–11**, and **16–18**. Thus the

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